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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,696	12/27/2001	Masahiko Tamura	TAMURA=4A	9284

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER

MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,696	TAMURA ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 December 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/117,379.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, IDS, STATUS OF HE APPLICATION AND CLAIMS

1. This application is a Divisional of Application No. 09/117,379 having a filing date of 7/29/98, now U.S. Patent No. 6,342,477, which claims benefit of application filed under 35 U.S.C. 371 having a filing date of 2/3/97 of PCT/JP97/00255.

Acknowledgment is made of Applicant's claim for priority based on Japanese Application No. 16701/1996 having a filing date of 2/1/96. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file of parent application Serial No. 09/117,379. With respect to the Information Disclosure Statements (IDS) and Form PTO-1449 filed 12/27/01, the references cited therewith on Form PTO1449 are not provided in the instant application. However, as per Applicant's request, since the cited references were considered previously in the parent application Serial No. 09/117,379; pursuant to 37 CFR § 1.98(d), the references cited in Form PTO-1449 in this application have been considered and signed as requested by Applicant. Claims 1-20 are present for examination.

CLAIMS REJECTION-35 U.S.C. 112 ^{1st} PARAGRAPH.

2. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing blood platelet formation in a patient suffering from thrombocytopenia by administering a parathyroid hormone (PTH), wherein the PTH is PTH (1-84) and PTH (1-34), does not reasonably provide

enablement for administering all other derivatives of PTH for increasing blood platelet formation in patients suffering from thrombocytopenia purpura (claim 5), suffering from selective suppression of megakaryocytes (claim 6), has been or is being treated with phenylbutazone, gold compounds, tolbutamide and chemotherapeutics (claim 7), suffering from a viral infection (claim 8), suffering from aplastic anemia (claim 9), suffering from osteomyelodysplasia syndrome (claim 10), suffering from leukemia (claim 11), and suffering from multiple myeloma (claim 12). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification teaches how to use PTH (1-84) and PTH (1-34) in a method for increasing blood platelet formation in a patient as disclosed in Figures 1-4 and Examples 1-4. Figures 1-4 show the platelet increasing action of PTH at various frequencies of administration time and dosages and Examples 1-4 demonstrate the preparation of drug solution to be administered thereof as disclosed in Figures 1-4, respectively. However, the scope of the instantly claimed invention are very broad and speculative in that the various PTHs and their derivatives as claimed can represent virtually any parathyroid hormone, and as such, the scope of the claims are extremely broad and relate to a very large number of possible PTHs of which some of them are not functional. For support, see the reference of Meytes et al. (J. Clin. Invest., Vol. 67, pp. 1263-1269, 1995) which teaches the effect of PTH on erythropoiesis and particularly on page 1265 states that not all the "derivative" of PTH exhibit the desired biological activity. Further, there is no working examples or data or evidence which shows that

the claimed PTHs and their derivatives are useful as a pharmaceutical composition for the intended purposes of increasing blood platelet formulation in patients suffering from the various disease conditions and situations as recited in claims 6-12.

Therefore, there is no evidence in the instant specification to use or administer the pharmaceutical formulations in therapeutically effective amount as claimed, except for the mere recitation of protocols on pages 6-9 and 16-17 in the instant specification disclosing the range of effective dosages of a pharmaceutical composition to be administered in various route for the intended purpose of increasing blood platelet formation in various disease conditions and situations as claimed in claims 6-12.

Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical compositions of claims 1-4 and 13-20 in the manner claimed. Hence, the only support for the claimed method and using the compositions thereof in the specification is Applicant's supposition of the invention as recited in the protocols.

Furthermore, Applicant's claims are directed to a very large number of PTH and their derivatives by using specific therapeutically effective amount of pharmaceutical formulation thereof, and there is no objective factual evidence in the specification showing that blood platelet formation has increased using the specific therapeutically effective amount of pharmaceutical composition claimed. Thus, one of ordinary skill in the art cannot administer specific effective amount of the pharmaceutical composition in all situations claimed without appropriate testing.

Therefore, in view of the above and in view of Meytes et al. reference, it would include those that have not been shown or taught to be useful or enabled by the

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disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since a vast range of pharmaceutical composition in all kinds possible PTH and their derivatives are contemplated and are encompassed as well as a wide range of treating various disease situations. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Hence, one of ordinary skill in the art would not be able to identify all the pharmaceutical preparations with wide range of dosages intended to be effective for the claimed purposes as encompassed in the claims would be effective and under what conditions. Thus, the claims are based on pure speculation that the method would be effective since Applicant has not established any *nexus* between an effective amount of the claimed PTH and its derivatives and their use in the manner claimed.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, *id.* At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation include (1) the

quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for administering all kinds of PTHs and their derivatives for increasing blood platelet formation in patients suffering from the various disease conditions and situations recited in claims 6-12. Thus, applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working example(s) or data or evidence, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIMS REJECTION-35 U.S.C. § 112^{2nd} PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said therapy" in lines 2, 4 and 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is indefinite and confusing in the recitation "wherein said PTH or PTH derivative is selected from the groups (a) to (c):" because the groups (a) to (c) are not recited in the claim. Appropriate correction is required.

Claim 1 is indefinite in the recitation "substituted in the 8-position, 16-position and/or 34-position" because the claim contains the use of an alternative expression wherein the limitation covers three different elements, i.e., "8-position", or "16-position" is not the same as "34-position" and vice versa. Thus, amendment of the claim to recite "substituted in the 8-position or 16-position or 34-position" or "substituted in the 8-position, 16-position and 34-position" is suggested.

Claim 1 is indefinite in the recitation "may be substituted" because this phrase makes the substitution "optional". If an ingredient, a step, or other structural element is truly optional (e.g., may be substituted), i.e., its presence is not necessary for attainment of the result that is an object of the invention, then recitation thereof does not belong in the claim.

Claim 1 is indefinite and vague in the recitation "...is such that one or more...." because the exact number is neither clear nor ascertainable. Appropriate clarification is required.

Claim 2 is indefinite in the recitation "wherein said PTH or PTH derivative is administered along with polyethylene glycol" because it is not understood how a PTH or derivative thereof is administered along with PEG. Amendment of the claim to recite "wherein said PTH or PTH derivative modified with PEG and administered" is suggested (See e.g., page 7, last paragraph in the instant specification as well as claim 11 of U.S. Patent No. 6,342,477 which is parent application of the instant application).

Claim 4 is also indefinite in the recitation "wherein said PTH or derivative is administered in a form incorporated in a sheet of gel. Amendment of the claim to recite "wherein said PTH or PTH derivative is incorporated in a sheet of gel is suggested (See e.g., claim 13 of U.S. Patent No. 6,342,477 which is parent application of the instant application).

Claims 6 and 8-12 are inconsistent with claim 5 in the recitation "wherein said patient is one suffering from". Amendment of the claims to recite "wherein said patient is a patient suffering from...." is suggested (See e.g., claim 5).

Claim 15 is indefinite in the recitation "systemically at a frequency.....". Amendment of the claim to recite ".....administered systemically at a frequency....." is suggested (See e.g., claim 4 of U.S. Patent No. 6,342,477 which is parent application of the instant application).

Similarly claim 16 is indefinite in the recitation "administered once every two weeks to once daily". Amendment of the claim to recite "administered from once every two weeks to once daily" (See e.g., claim 5 of U.S. Patent No. 6,342,477 which is parent application of the instant application).

CLAIMS REJECTION-35 U.S.C. § 103(a)

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benigni et al. (Am. J. Nephrol., Vol. 5, pp. 243-247, 1985) taken with Stedmann's Medical Dictionary, 26th Ed., M. Spraycar, editor, William & Wilkins, Baltimore, page 1808, 1995 and Krstenansky et al. (U.S. Patent No. 5,589,452).

The reference of Benigni et al. is directed generally to teach that various concentrations of PTH and its derivative inhibit the human platelet aggregation. To the extent that the platelet counts are concerned, use of PTH has clearly inhibited platelet

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aggregation in human (See pages 243-247) as directed to claims 1 and 13-14. Further, on page 1808 Stedmann's Medical Dictionary discloses that thrombocytopenia is "A condition in which there is an abnormally small number of platelets in the circulating blood". Thus, thrombocytopenia is the result of failure of platelet production. Therefore, inhibiting platelet aggregation is expected to result in an increase in the number of circulating platelet, an ordinary skill in the art at the time the invention was made would have expected to the same agent (PTH) for treating patients having disorders due to having a small number of circulating blood platelets with the expectation of success.

With respect to the limitations of modifying the active ingredient PTH with PEG, encapsulating with microcapsule and incorporating in a sheet of gel as claimed in claims 2-4, as acknowledged on pages 7-8 in the instant specification a typical dosage form for the pharmaceutical drugs of the invention is as an injection (e.g., liquid preparations and lyophilized preparations) that is produced by ordinary pharmaceutical formulation procedure applicable to peptides; also useful are dosage forms that are intended to show local and delayed actions, as by inclusion within microcapsules or incorporation in sheets of gel. When formulating pharmaceutical preparations, pharmaceutically acceptable adjuvants may be added. In order to increase the half-life in blood, pharmaceutical preparations modified with PEG may be formulated. Further, on page 8, the reference states that the amounts in which the adjuvants are to be used may be selected as appropriate for the dosage form and other factors from within the ranges tolerated by pharmaceutical formulation procedures. Thus, as acknowledged in the instant specification and as known in the art, the selection of the appropriate process

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conditions would have been *prima facie* obvious because where the general conditions of a claim is known in the art, it is not inventive to discover the optimum conditions. Therefore, it is within the ordinary skill of the art to modify the active ingredient PTH with PEG, encapsulate the PTH with microcapsule and incorporate the PTH in a sheet of gel in the manner claimed in claims 2-4.

In regard to the specific dosages, frequency of administration and route of administration as claimed in claims 15-20, the reference of Krstenansky et al. teaches the administration of PTH and its derivative for the prophylaxis and treatment of osteoporosis in mammals in an amounts between about 0.01 and 1 $\mu\text{g}/\text{kg}$ body weight per day, preferably from about 0.07 to about 0.2 $\mu\text{g}/\text{kg}$ body weight per day. For 50 kg human female subject, the daily dose of active ingredient is from about 0.5 to about 50 μg s, preferably from about 3.5 to about 10 μg s which overlaps with the claimed ranges of 1 μg to 1,000 μg of claim 15 and 5 μg to 200 μg of claim 16. In other mammals, such as horses, dogs, and cattle, higher doses may be required. This dosage may be delivered in a conventional pharmaceutical composition by a single administration, by multiple application, or via controlled release, as needed to achieve the most effective results, preferably one or more times daily by injections. The selection of exact dose and composition and the most appropriate delivery regimen will be influenced by the pharmacological properties of the selected polypeptide, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient. Representative delivery regimens include oral, parenteral (including subcutaneous, intramuscular, and intravenous), rectal, buccal (including sublingual), transdermal, and

intranasal (See col. 15, lines 1-20) as directed to claims 15-20. Although, the reference teaches the administration of PTH for treatment of osteoporosis, nevertheless, the reference discloses the specific dosages, frequency of administration and route of administration of PTH, and as such, it is within the purview of one of ordinary skill in the art to optimize dosages, duration of the dosages and route of administration in the manner claimed in claims 15-20. Further, as acknowledged on page 8, last paragraph to page 9 first paragraph in the instant specification by stating that it is within the ordinary skill of the art of clinical physician to adjust or optimize the desired workable dosages, frequency of administration and route of administration by routine experimentation because the specific dose level for any particular patient will depend on the etiology of the disease. Also depends on the time of administration, the route of administration, synergistic effects with any other drugs being administered and the degree of protection being sought. Further, the administration can be repeated at suitable intervals if necessary.

Therefore, in view of the above and in view of the combined teachings of the prior art at the time the invention was made one of ordinary skill in the art would have been motivated to employ the method for increasing blood platelet formation in a patient by administering to said patient PTH or PTH derivative wherein said PTH or PTH derivative is modified with PEG, encapsulated within microcapsules, incorporated in a sheet of gel and administered parenterally at various dosages and intervals. Thus, the combined teachings of the prior art makes obvious the claimed invention for the reasons

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discussed above, absent of objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDENCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

AM Mohamed/AAM

January 26, 2004

Christopher S. F. Low
CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1800